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1. Your reference AP9

2. Patent application number 12 AUG 1999
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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Angiogene Pharmaceuticals Ltd
14 PLOWDEN PARK
ASTON ROWANT
OXON OX9 5SX

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation U.K. 7244780011

4. Title of the invention

NEW STILBENES WITH VASCULAR DAMAGING ACTIVITY

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

10 ASTON PARK
ASTON ROWANT
OXON OX9 5SW

Patents ADP number *(if you know it)*

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NEW STILBENES WITH VASCULAR DAMAGING ACTIVITY

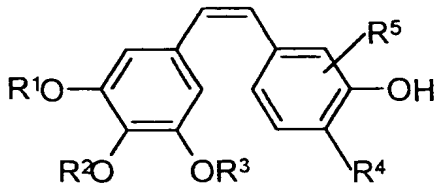
Formation of new vasculature by angiogenesis is a key pathological feature of several diseases (J Folkman, New England Journal of Medicine 333, 1757-1763 (1995)). For example, for a solid tumour to grow it must develop its own blood supply upon which it depends critically for the provision of oxygen and nutrients; if this blood supply is mechanically shut off the tumour undergoes necrotic death. Neovascularisation is also a clinical feature of skin lesions in psoriasis, of the invasive pannus in the joints of rheumatoid arthritis patients and of atherosclerotic plaques. Retinal neovascularisation is pathological in macular degeneration and in diabetic retinopathy. In all these diseases reversal of neovascularisation by damaging the newly-formed vascular endothelium is expected to have a beneficial therapeutic effect.

Attacking the tumour vasculature has several important advantages over a direct attack on the tumour. In particular the endothelial cells of the vasculature are more genetically stable than those of the tumour itself and are therefore unlikely to become resistant to the damaging agent. Thus a major problem in conventional anti-tumour therapy, that of drug resistance, is circumvented by this approach. Furthermore, since the endothelial cells of the tumour vasculature, unlike the tumour cells themselves, are similar between different solid tumour types, vascular damaging agents are able to attack the tumour regardless of its origin and location.

A number of tubulin-binding agents including combretastatin A4 and its phosphate prodrug (D.J. Chaplin et al, Anticancer Research 19, 189-196, (1999)) are known to selectively damage neovasculature of solid tumours in animal models. While there are reports of the activity of analogues of combretastatin A4 in tubulin binding assays, in cytotoxicity assays and in tumour models there have been no reports of the vascular damaging activities of analogues. Since the activity of tubulin-binding compounds against *in vitro* assays are poor predictors of selective vascular damaging activity and activity of such compounds *in vivo* can also be mediated by direct antimitotic effects on the tumour itself, no prediction can be made of the selective vascular damaging activity of known or novel analogues of the combretastatins from published reports. Thus compounds which have the advantages of a selective anti-vascular mechanism given above, rather than acting through a direct effect on the tumour tissue itself, are not apparent.

We have found a series of novel stilbenes with vascular damaging activity. These compounds specifically damage newly-formed vascular endothelium, especially that associated with solid tumours, without affecting the normal, established vascular endothelium of the host species. Such compounds are of use in the prophylaxis and treatment of cancers involving solid tumours and in other diseases where there is inappropriate formation of new vasculature such as diabetic retinopathy, psoriasis, rheumatoid arthritis, macular degeneration and the formation of atherosclerotic plaques.

Thus according to one aspect of the invention we provide a compound of formula (1):



(1)

Wherein:

R1,R2 and R3 are each independently hydrogen, alkyl, haloalkyl or cycloalkyl

R4 is optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, haloalkoxy, alkylthio, haloalkylthio, alkylsulphinyl, alkylsulphonyl, nitro, cyano, halo, amino, alkylamino, dialkylamino, alkanoyl, heteroaryl, heterocycloalkyl, carboxyl, alkoxycarbonyl, alkoxycarbonyloxy, alkoxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylcarbonylamino, aminosulphonyl, alkylaminosulphonyl, dialkylaminosulphonyl, alkylsulphonylamino, aminosulphonylamino, alkylaminosulphonylamino, dialkylaminosulphonylamino or mercapto

R5 is hydrogen, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, alkylthio, haloalkylthio, alkylsulphinyl, alkylsulphonyl, nitro, cyano, halo, amino, alkylamino, dialkylamino, alkanoyl, heteroaryl, heterocycloalkyl, carboxyl, alkoxycarbonyl, alkoxycarbonyloxy, alkoxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylcarbonylamino, aminosulphonyl, alkylaminosulphonyl, dialkylaminosulphonyl, alkylsulphonylamino, aminosulphonylamino, alkylaminosulphonylamino, dialkylaminosulphonylamino or mercapto

and the pharmaceutically acceptable salts, solvates, hydrates and prodrugs thereof.

As used herein the term "alkyl", alone or in combinations, means a straight or branched-chain alkyl group containing from one to seven, preferably a maximum of four, carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl and pentyl. Examples of alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy and t-butoxy.

Optionally substituted alkoxy groups, optionally substituted alkyl groups and optionally substituted cycloalkyl groups may bear one or more substituents independently selected from halogen, hydroxy, amino, alkylamino, dialkylamino, alkoxy, alkylthio, alkylsulphonyl, carboxyl, mercapto, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, alkylcarbonyl(alkyl)amino, alkoxycarbonylamino, sulphate and phosphate.

The term "halogen" means fluorine, chlorine, bromine or iodine.

An alkenyl group may be for example an olefinic group containing from two to seven carbon atoms for example methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene and t-butylene. An alkynyl group may be for example an ethynyl , propynyl or butynyl group.

The term heteroaryl is defined herein as a mono- or bi-cyclic aromatic group containing one to four heteroatoms selected in any combination from N, S or O atoms. Examples of heteroaryl groups include pyridyl, pyrimidyl, furyl, thienyl, pyrrolyl , pyrazolyl, indolyl, benzofuryl, benzothienyl, benzothiazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, quinolyl and isoquinolyl groups.

The term heterocycloalkyl includes heterocycloalkyl groups containing 3-6 carbon atoms and one or two oxygen, sulphur or nitrogen atoms. Particular examples of such groups include azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, morpholinyl or thiomorpholinyl groups.

The term cycloalkyl means a cycloaliphatic group containing 3-10 carbon atoms such as, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

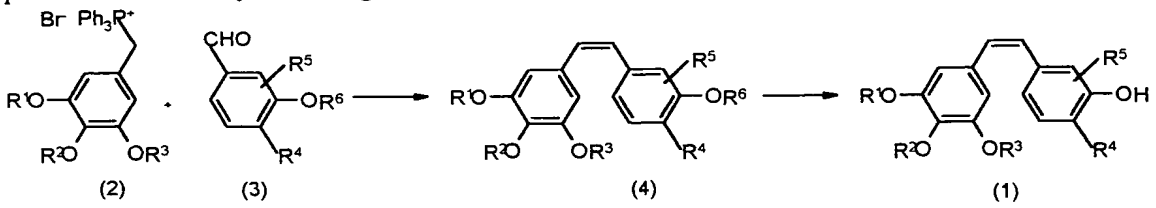
Where one or more functional groups in compounds of formula (1) are sufficiently basic or acidic the formation of salts is possible. Suitable salts include pharmaceutically acceptable salts for example acid addition salts including hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates and tartrates, salts derived from inorganic bases including alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and salts derived from organic amines such as morpholine, piperidine or dimethylamine salts.

Those skilled in the art will recognise that compounds of formula (1) may exist as stereoisomers and/or geometrical isomers and accordingly the present invention includes all such isomers and mixtures thereof.

Suitable prodrugs include esters, phosphates, sulphates, amides, carbamates and carbonates.

Compounds of the invention can be prepared by any process known to a person skilled in the art. Compounds of formulae (1) can be prepared by a number of processes as generally described hereinbelow and more specifically in the Examples hereinafter. In the general preparations described below it may be necessary to employ protecting groups which are then removed during the final stages of the synthesis. The appropriate use of such protecting groups and processes for their removal will be readily apparent to those skilled in the art. In the following process description, the symbols R1, R2, R3, R4 and R5, when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated

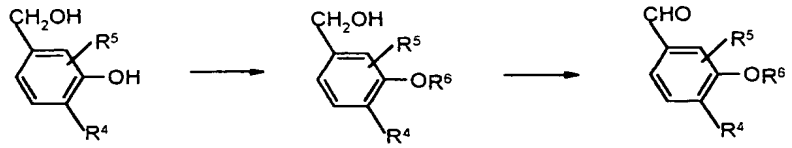
In one general example compounds of formula (1) can be prepared by Wittig olefin synthesis involving reaction of a phosphonium salt of formula (2) with a strong base, for example an alkyllithium such as n-butyllithium or t-butyllithium or a metal hydride such as sodium hydride in a solvent such as an ether solvent for example diethyl ether or tetrahydrofuran or in a solvent such as a hydrocarbon solvent for example toluene at a temperature of between about -100°C to about 30°C followed by treatment with an aldehyde of formula (3) in which R6 is a protecting group, to give an intermediate of formula (4). The synthesis of compounds of formula (1) is then completed by removal of the group R6. Suitable protecting groups R6 include trialkylsilyl, for example t-butyldimethylsilyl, and allyl. Where R6 is a trialkylsilyl group it may be removed, for example, by treatment with a quaternary ammonium fluoride such as tetrabutylammonium fluoride in an ether solvent such as tetrahydrofuran at a temperature of about -30°C to about 40°C conveniently at or near ambient temperature. Where R6 is an allyl group it may be removed for example by treatment with a palladium(0) complex such as tetrakis(triphenylphosphine)Pd(0) in a solvent such as a chlorinated solvent, for example dichloromethane, at a temperature of about -40°C to about 40°C conveniently at or near ambient temperature, in the presence of an allyl scavenger such as morpholine.



(2) (3) (4) (1)

Aldehydes of formula (3) can be prepared by any process known to a person skilled in the art. In one general example an aldehyde of formula (3) can be prepared from an alcohol of formula (5) by oxidation with a suitable oxidising agent. Suitable oxidising agents include the Dess-Martin reagent and manganese dioxide. Alcohols of formula (5) can be prepared by application of standard methods of organic synthesis including the selective protection of phenols of formula (6). Where the protecting group R6 is a trialkylsilyl group, for example t-butyldimethylsilyl, alcohols of formula (5) may be prepared, for example, by treatment of a phenol of formula (6) with a strong base, for example an alkyllithium such as n-butyllithium or t-butyllithium or a metal hydride such as sodium hydride in a solvent such as an ether solvent for example diethyl ether or tetrahydrofuran or in a solvent such as a hydrocarbon solvent for example toluene at a temperature of between about -100°C to about 40°C followed by treatment with *tert*-butylchlorodimethylsilane.

Phenols of formula (6) are either known or may be prepared from known compounds using standard methods of organic synthesis.



(6) (5) (3)

Compounds of formula (1) may also be prepared from other compounds of formula (1) by chemical modification. Examples of such chemical modifications that may be applied are standard alkylation, heteroarylation, acylation, thioacylation, sulphonylation, sulphation, phosphorylation, aromatic halogenation, aromatic nitration and coupling reactions. These reactions may be used to add new substituents or to modify existing substituents. Alternatively, existing substituents in compounds of formula (1) may be modified by, for example, oxidation, reduction, elimination, hydrolysis or other cleavage reaction to yield other compounds of formula (1).

Compounds according to the invention are able to destroy tumour vasculature and vasculature that has been newly formed while leaving unaffected normal, mature vasculature. The ability of the compounds to act in this way may be determined by the tests described hereinafter.

The compounds according to the invention are thus of particular use in the prophylaxis and treatment of cancers involving solid tumours and in the prophylaxis and treatment of diseases where inappropriate angiogenesis occurs such as diabetic retinopathy, psoriasis, rheumatoid arthritis, atherosclerosis and macular degeneration.

The compounds of the invention may be administered as a sole therapy or in combination with other treatments. For the treatment of solid tumours compounds of the invention may be administered in combination with radiotherapy or in combination with other anti-tumour substances for example those selected from mitotic inhibitors, for example vinblastine, paclitaxel and docetaxel; alkylating agents, for example cisplatin, carboplatin and cyclophosphamide; antimetabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea; intercalating agents for example adriamycin and bleomycin; enzymes, for example aspariginase; topoisomerase inhibitors for example etoposide, topotecan and irinotecan; thymidylate synthase inhibitors for example raltitrexed; biological response modifiers for example interferon; antibodies for example edrecolomab: and anti-hormones for example tamoxifen. Such combination treatment may involve simultaneous or sequential application of the individual components of the treatment.

For the prophylaxis and treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions selected with regard to the intended route of administration and standard pharmaceutical practice. Such pharmaceutical compositions may take a form suitable for oral, buccal, nasal, topical, rectal or parenteral administration and may be prepared in a conventional manner using conventional excipients. For example for oral administration the pharmaceutical compositions may take the form of tablets or capsules. For nasal administration or administration by inhalation the compounds may be conveniently delivered as a powder or in solution. Topical administration may be as an ointment or cream and rectal administration may be as a suppository. For parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) the composition may take the form of, for example, a sterile solution, suspension or emulsion.

The dose of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, the route of administration, the form and severity of the condition and whether the compound is to be administered alone or in combination with another drug. Thus the precise dose will be determined by the administering physician but in general daily dosages may be in the range 0.001 to 100mg/kg preferably 0.1 to 10mg/kg.

BIOLOGICAL ACTIVITY

The following tests were used to demonstrate the activity and selectivity of compounds according to the invention.

Activity against tumour vasculature measured by fluorescent dye.

The following experiment further demonstrates the ability of the compounds to damage tumour vasculature.

Tumour functional vascular volume in CaNT tumour-bearing mice was measured using the fluorescent dye Hoechst 33342 according to the method of Smith *et al* (Brit J Cancer **57**, 247-253, 1988). Five animals were used in control and treated groups. The fluorescent dye was dissolved in saline at 6.25 mg/ml and injected intravenously at 10 mg/kg 24 hours after intraperitoneal drug treatment. One minute later, animals were killed and tumours excised and frozen; 10 μm sections were cut at 3 different levels and observed under UV illumination using an Olympus microscope equipped with epifluorescence. Blood vessels were identified by their fluorescent outlines and vascular volume was quantified using a point scoring system based on that described by Chalkley, (J Natl Cancer Inst, **4**, 47-53, 1943). All estimates were based on counting a minimum of 100 fields from sections cut at the 3 different levels.

Activity against tumour vasculature measured by radioactive tracer.

The following experiment demonstrates the ability of the compounds to damage selectively tumour vasculature.

Subcutaneous CaNT tumours were initiated by injecting 0.05ml of a crude tumour cell suspension, approximately 10^6 cells, under the skin overlying the rear dorsum of 12-16 week-old mice. The animals were selected for treatment after approximately 3-4 weeks, when their tumours reached a geometric mean diameter of 5.5-6.5mm. Compounds were dissolved in sterile saline and injected intraperitoneally in a volume of 0.1 ml per 10 g body weight. Tumour perfusion was measured 6 hours after intraperitoneal administration in tumour kidney, liver, skin muscle, gut and brain by the ^{86}RbCl extraction technique (Sapirstein, Amer J Physiol, **193**, 161-168, 1958). Tissue radioactivity measured 1 minute after an intravenous injection of ^{86}RbCI was used to calculate relative blood flow as a proportion of cardiac output (Hill and Denekamp, Brit J Radiol., **55**, 905-913, 1982). Five animals were used in control and treated groups. Results were expressed as a percentage of the blood flow in the corresponding tissues in vehicle treated animals. Compounds of the invention were able to reduce tumour blood flow by more than 50% at doses of 100mg/kg or below without significant reduction in the blood flow of kidney, liver, skin, muscle, gut or brain.

The following non-limiting Examples illustrate the invention:

EXAMPLE 1
1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

A solution of 1-(3-*tert*-butyldimethylsilyloxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (491mg) in anhydrous tetrahydrofuran (10ml) at room temperature was treated slowly with a 1.1M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.1ml). After 30 minutes crushed ice (5ml) and diethylether (30ml) were added and the aqueous phase extracted with diethylether (5 portions of 5ml). The combined extracts were washed with water (3 portions of 10ml) and brine (10ml), dried (MgSO4) and concentrated under reduced pressure to give a solid. Recrystallisation from ethyl acetate/hexane gave the title compound (208mg) as a white solid m.p. δH (d6-DMSO) 2.07 (s, 3H), 3.57 (s, 6H), 3.62 (s, 3H), 6.40 (d, J = 12Hz, 1H), 6.46 (d, J = 12 Hz, 1H), 6.56 (s, 2H), 6.61 (dd, J = 8Hz, 2Hz, 1H), 6.76 (d, J= 1.7Hz, 1H), 6.98 (d, J = 8Hz, 1H), 9.21 (s 1H).

The 1-(3-*tert*-butyldimethylsilyloxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene used as starting material in the above preparation was prepared as follows:
A suspension of 3,4,5-trimethoxybenzyltriphenylphosphonium bromide (848mg) in dry tetrahydrofuran (50ml) at -78°C was treated dropwise with n-butyllithium (0.9ml of a 1.8M solution in hexane) and the mixture allowed to warm to -40°C and stir for 1h. The mixture was recooled to -78°C and a solution of 3-*tert*-butyldimethylsilyloxy-4-methylbenzaldehyde (390mg) in tetrahydrofuran (40ml) added slowly. After a further 2h the mixture was allowed to warm to room temperature before being poured into ice water (20ml). The aqueous phase was extracted with diethylether (5 portions of 20ml) and the combined extracts were washed with water (3 portions of 20ml) and brine (2 portions of 20ml), dried (MgSO4) and concentrated under reduced pressure to give an oil. Purification by chromatography on silica gel, eluting with petroleum ether / ethyl acetate (90:10) gave 1-(3-*tert*-butyldimethylsilyloxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (456mg) as a red oil.

The 3-*tert*-butyldimethylsilyloxy-4-methylbenzaldehyde used as starting material in the above preparation was prepared as follows:
A solution of Dess-Martin periodinane (187mg) in dichloromethane (4ml) was treated slowly with a solution of 3-*tert*-butyldimethylsilyloxy-4-methylbenzyl alcohol (100mg) in dichloromethane (4ml) and the mixture stirred for 1h at room temperature. Diethylether (10ml) was added followed by aqueous sodium thiosulphate solution (10ml) and the mixture stirred for 15 minutes. The aqueous phase was extracted with diethylether (5 portions of 20ml) and the combined extracts were washed with aqueous sodium thiosulphate solution (3 portions of 10ml), water (3 portions of 10ml) and brine (2 portions of 10ml), dried (MgSO4) and concentrated under reduced pressure to give a yellow solid. Purification by chromatography on silica gel, eluting with petroleum ether / diethyl ether (50:50) gave 3-*tert*-butyldimethylsilyloxy-4-methylbenzaldehyde (85mg).

The 3-*tert*-butyldimethylsilyloxy-4-methylbenzyl alcohol used as starting material in the above preparation was prepared as follows:
A solution of 3-hydroxy-4-methylbenzyl alcohol (275mg) in dry tetrahydrofuran (15ml) at -78°C was treated slowly with n-butyllithium (1.2ml of a 1.8M solution in hexane) and the mixture stirred for 15minutes before being allowed to warm to room temperature and stir for a further 30minutes. A solution of *tert*-butylchlorodimethylsilane (287mg) in tertrahydrofuran (10ml) was added and the mixture stirred for 16h. Water (20ml) was added and the mixture extracted with diethylether (5 portions of 20ml) and the combined extracts were washed with water (2 portions of 10ml) and brine (20ml), dried (MgSO4) and concentrated under reduced pressure. Purification by chromatography on silica gel, eluting with petroleum ether / diethyl ether (50:50) gave 3-*tert*-butyldimethylsilyloxy-4-methylbenzyl alcohol (390mg).